**UNITED STATES ENVIRONMENTAL PROTECTION AGENCY**
**WASHINGTON, D.C. 20460**

**OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION**

[ SEQ CHAPTER \h \r 1]**MEMORANDUM**

**Date:** December 17, 2012

**SUBJECT:** Dicamba and Dicamba Metabolites DCSA and DCGA.
Joint Review of Toxicology Studies.

**PC Code:** 128931
**Decision No.:** 432752
**Petition No.:** N/A
**Risk Assessment Type:** N/A
**TXR No.:** 0055497
**MRID No.:** See list

**DP Barcode:** D381800
**Registration No.:** 00524-00582
**Regulatory Action:** N/A
**Case No.:** 0065
**CAS No.:** 1040440-79-1
**40 CFR:** 180.227

Ver.Apr. 2010

**FROM:** [ SEQ CHAPTER \h \r 1]Kit Farwell, DVM, DABT
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**THROUGH:** Michael Metzger, Branch Chief
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**TO:** Michael Walsh, Reviewer / PM Team 23
Kathryn Montague, PM 23
Herbicide Branch
Registration Division (7505P)

The toxicity database for newly completed studies with dicamba and dicamba metabolites, 3,6-dichlorosalicylic acid (DCSA) and 3,6-dichlorogentisic acid (DCGA), is attached.

This was a global review with Canada and Japan as part of a tolerance petition for a new use of dicamba on dicamba tolerant soybean forage and hay. The study summaries were prepared by the registrant and had data tables added by the HED toxicology contractor. Responsibility for the primary review of these studies was with the Health Effects Division of the USEPA and secondary review was by the Pest Management Regulatory Agency of Canada and the Food

Safety and Consumer Affairs Bureau of Japan. Comments from the global partners were considered by the USEPA and incorporated into the final version of the study summaries.

The following table lists the study type, MRID, year of the study, results, study classification according to HED criteria, and the page of the attached monograph where the review is located.

| Study Type Chemical | MRID (year) | Results | Classification | Page |
|---|---|---|---|---|
| 870.1100<br>DCSA<br>Acute Oral Toxicity | 47899504 (2007) | $LD_{50}$ = 2641 mg/kg | Acceptable/ Guideline | 3 |
| 870.1100<br>DCGA<br>Acute Oral Toxicity | 47899505 (2009) | $LD_{50}$ = 1460 mg/kg | Acceptable/ Guideline | 7 |
| 870.3050<br><br>DCGA<br>Subchronic Tox - Rat (28 days) | 47899506 (2009) | Included FOB and motor activity<br>0, 500, 3000, 6000, 12000 ppm<br>M: 0, 40, 240, 474, 956 mg/kg/day<br>F: 0, 45, 265, 519, 1063 mg/kg/day for females.<br>NOAEL = 474 mg/kg/day<br>LOAEL = 956 mg/kg/day based upon decr BW in males | Acceptable/ Guideline | 10 |
| 870.3100<br><br>DCSA<br>Subchronic Tox - Rat (90 days) | 47899507 (2009) | (500,3000, 6000, 12000 ppm).<br>M: 0, 32, 195, 362, 659 mg/kg/day<br>F: 0, 37, 222, 436, 719 mg/kg/<br>Crl:CD®[SD] rats. Included FOB and MA.<br>NOAEL = 362 mg/kg/day<br>LOAEL = 659 mg/kg/day based on decreased body weight, increased motor activity, decreased hematological parameters, and increased liver enzymes | Acceptable/ Guideline | 19 |
| 870.3150<br><br>DCSA<br>Subchronic Tox – Dog (90 days) | 48358002 (2011) | 0, 15, 50 and 150 mg/kg/day. 90-day capsule study.<br>NOAEL = 50 mg/kg/day<br>LOAEL = 150 mg/kg/day based on mortality, decreased body weight, clinical signs (abnormal excreta and emesis), and increased clotting time. | Acceptable/ Guideline | 33 |
| 870.3700a<br><br>DCSA<br><br>Developmental - Rat | 47899519 (2007)<br><br>47899518 (range-finding) | 0, 10, 30, 100 mg/kg/day (GD 6-19). Crl:CD(SD) rats<br>Maternal NOAEL: 100 mg/kg/day, highest dose tested<br>Maternal LOAEL: not attained<br>Developmental NOAEL: 100 mg/kg/day, highest dose tested<br>Developmental LOAEL: not attained<br>Classified acceptable/guideline when considered with rangefinding study.<br>Rangefinding study: MRID 47899518.<br>0, 50, 200, 500 or 1000 mg/kg/day: 8 females/dose<br>200 mg/kg/day: clinical signs (rales, red/clear material on body), decr fetal wt<br>500 mg/kg/day: mortality, early resorptions in all survivors | Acceptable/ Guideline | 43<br><br>49 |

| Study Type<br>Chemical | MRID<br>(year) | Results | Classification | Page |
|---|---|---|---|---|
| 870.3700a<br><br>DCGA<br>Developmental<br>Rat Rangefinding<br>study | 47899520<br>(2009) | 0, 50, 200, 500, 1000 mg/kg/day<br>Maternal: 200 mkd: Signs of rales, clear material on body<br>500 mkd: BW 4.0-6.6% lower GD 13-20<br>1000 mkd: Mortality. BW 4.4-12.1% lower GD 12-20<br>Developmental: No effects on uterine growth, survival, external malformations or variations. Fetuses received external exam only, no skeletal examination. | Acceptable/<br>Guideline | 51 |
| 870.3700b<br><br>DCSA<br>Developmental<br>- Rabbit | 47899522<br>(2009)<br><br>47899521<br>(2010) | 0, 10, 25, 65 mg/kg/day (GD 6-28). NZW rabbits<br>Maternal NOAEL: 65 mg/kg/day, highest dose tested.<br>Maternal LOAEL: not attained<br>Developmental NOAEL: 65 mg/kg/day, highest dose tested.<br>Developmental LOAEL: not attained<br>Classified acceptable/guideline when considered with rangefinding study.<br>Rangefinding study: MRID 47899521<br>0, 10, 30, 100, 300 mg/kg/day. 6 females/dose. 300 mg/kg/day was lethal dose | Acceptable/<br>Guideline | 57<br><br><br><br><br><br>63 |
| 870.3800<br><br>DCSA<br>Reproduction and<br>fertility effects<br>- Rat | 47899517<br>(2009) | (0, 50, 500, 5000 ppm)<br>M: 0, 4, 37, 362 mg/kg/day ($F_0$ generation)<br>F: 0, 4, 43, 414 mg/kg/day ($F_0$ generation)<br>Crl:CD(SD) rats<br>Parental NOAEL = 500 ppm (37 mg/kg/day)<br>Parental LOAEL = 5000 ppm (362 mg/kg/day) based upon decreased body weight.<br>Repro NOAEL = 5000 ppm (362 mg/kg/day), highest dose tested.<br>Repro LOAEL: Not attained.<br>Offspring NOAEL = 50 ppm (4 mg/kg/day)<br>Offspring LOAEL = 500 ppm (37 mg/kg/day) based upon decreased pup body weight in $F_1$ pups on postnatal days 14 and 21.<br>At 5000 ppm, high incidence of pup mortality | Acceptable/<br>Guideline | 64 |
| 870.4200a<br><br>DCSA<br>Chronic Toxicity/<br>Carcinogenicity<br>-Rat | 47899516<br>(2009)<br><br>48358003<br>(2011) | (0, 10, 100, 300, 1000, 3000 ppm)<br>M: 0.5, 5.0, 14.6, 48.8, and 150.1 mg/kg/day<br>F" 0.6, 6.1, 18.4, 60.9, and 181.5 mg/kg/day<br>Crl:CD®[SD] rats<br>NOAEL = 150 mg/kg/day, highest dose tested. Not carcinogenic.<br>LOAEL: Not established | Acceptable/<br>Guideline | 83 |
| 870.5100<br>DCSA<br>Bacterial gene<br>mutation | 47899509 | Did not induce gene mutation | Acceptable/<br>Guideline | 93 |
| 870.5100<br>DCGA<br>Bacterial gene<br>mutation | 47899514 | Did not induce gene mutation | Acceptable/<br>Guideline | 101 |
| OPPTS 870.5100<br>Dicamba<br>Bacterial gene<br>mutation | 47899525 | Did not induce gene mutation | Acceptable/<br>Guideline | 111 |

| Study Type Chemical | MRID (year) | Results | Classification | Page |
|---|---|---|---|---|
| 870. 5300 DCSA HGPRT in Chinese hamster cells | 47899512 | Did not induce forward mutations at the HGPRT locus in CHO cells | Acceptable/ Guideline | 119 |
| 870. 5300 Dicamba HGPRT in Chinese hamster cells | 47899526 | Did not induce forward mutations at the HGPRT locus | Acceptable/ Guideline | 127 |
| 870.5375 DCSA Chromosome aberration assay in human lymphocytes | 47899510 | No conclusions can be reached; the data are inconclusive. | Unacceptable/ Non-guideline | 139 |
| 870. 5375 Dicamba Chromosomal aberration assay in human lymphocytes | 47899527 | The S9-activated portion of the assay should have been repeated; until then considered positive. | Acceptable/ Guideline | 151 |
| 870.5385 DCSA Chromosome aberration assay in rat bone marrow cells | 47899513 | Did not cause an increase in the number of chromosome aberrations in rat bone marrow cells | Acceptable/ Guideline | 161 |
| 870.5385 DCGA Chromosome aberration assay in rat bone marrow cells | 47899515 | Did not cause increased numbers of chromosome aberrations in rat bone marrow cells | Acceptable/ Guideline | 167 |
| 870. 5395 DCSA Micronucleus assay | 47899511 | Did not induce a clastogenic or aneugenic response in mouse bone marrow cells of male mice | Acceptable/ Guideline | 172 |
| 870. 5395 Dicamba Micronucleus assay | 47899528 | Was neither clastogenic nor aneugenic in mouse bone marrow | Acceptable/ Guideline | 178 |
| 870.6200<br><br>Dicamba Subchronic Tox / Subchronic Neurotox | 48358001 (2011) | (0, 500, 3000, 6000, 12000 ppm)<br>M: 0, 34, 197, 397, 803 mg/kg/day<br>F: 0, 39, 230, 458, 938 mg/kg/day<br>Crl:CD® [SD] rats<br>NOAEL = 397<br>LOAEL = 803 mg/kg/day based on CNS/behavioral signs (impaired equilibrium, rigid muscle tone, uncoordinated righting, decr hindlimb footsplay, unkempt appearance), gasping, rales, clinical pathology (inc WBC, lymphocytes, decr globulin, incr alkaline phosphatase) | Acceptable/ Guideline | 185 |

| Study Type<br>Chemical | MRID<br>(year) | Results | Classification | Page |
|---|---|---|---|---|
| 870.7485<br>DCSA Metabolism<br>(single dose) | 47899502<br>(2006) | (100 mg/kg)<br>Extensively absorbed and excreted rapidly in urine with little metabolism. | Acceptable/<br>Guideline | 193 |
| 870.7485<br>DCSA<br>Metabolism<br>(repeated doses) | 47899503<br>(2006) | (42, 125, 250, 375, or 500 mg/kg/day<br>Well absorbed and rapidly excreted in urine with minimal metabolism. | Acceptable/<br>Guideline | 200 |